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The Sicilian Gambit

A New Approach to the Classification of Antiarrhythmic Drugs Based on Their Actions on Arrhythmogenic Mechanisms

Task Force of the Working Group on Arrhythmias of
the European Society of Cardiology

The Queen's Gambit is an opening move in chess that provides a variety of aggressive options to the player electing it. This report represents a similar gambit (the Sicilian Gambit) on the part of a group of basic and clinical investigators who met in Taormina, Sicily to consider the classification of antiarrhythmic drugs. Paramount to their considerations were 1) dissatisfaction with the options offered by existing classification systems for inspiring and directing research, development, and therapy, 2) the disarray in the field of antiarrhythmic drug development and testing in this post–Cardiac Arrhythmia Suppression Trial (CAST) era, and 3) the desire to provide an operational framework for consideration of antiarrhythmic drugs that will both encourage advancement and have the plasticity to grow as a result of the advances that occur. The multifaceted approach suggested is, like the title of the article, a gambit. It is an opening rather than a compendium and is intended to challenge thought and investigation rather than to resolve issues. The article incorporates first, a discussion of the shortcomings of the present system for drug classification; second, a review of the molecular targets on which drugs act (including channels and receptors); third, a consideration of the mechanisms responsible for arrhythmias, including the identification of "vulnerable parameters" that might be most accessible to drug effect; and finally, clinical considerations with respect to antiarrhythmic drugs. Information relating to the various levels of information is correlated across categories (i.e., clinical arrhythmias, cellular mechanisms, and molecular targets), and a "spread sheet" approach to antiarrhythmic action is presented that considers each drug as a unit, with similarities to and dissimilarities from other drugs being highlighted. A complete reference list for this work would require as many pages as the text itself. For this reason, referencing is selective and incomplete. It is designed, in fact, to provide sufficient background information to give the interested reader a starting frame of reference rather than to recognize the complete body of literature that is the basis for this article. (*Circulation* 1991;84:1831–1851)

For two decades, the approach to antiarrhythmic drug development and administration has focused on the Vaughan Williams classification.[1–3] This classification, presented in Table 1, has been useful in teaching students and physicians because it is physiologically based, can be learned quickly, and facilitates discussion of the potentially beneficial or deleterious actions of drugs. The Vaughan Williams classification originated at a time when our knowledge of electrophysiological mechanisms (including the roles of receptors and channels) was less extensive than now and relatively few antiarrhythmic agents were available. In the ensuing years there has been a continuing attempt to fit new concepts about arrhythmias and about the actions of new agents into its general framework. However, the usefulness of this classification for basic investigators and clinicians is limited because it provides incomplete links among the actions of antiarrhythmic agents, the mechanisms of arrhythmias, and the efficacy of therapy.

Other limitations that have become increasingly visible are as follows:

1) The classification is a hybrid, such that classes I and IV represent block of ion channels; class II, block of receptors; and class III, a change in an electrophysiological variable (the action potential duration). In addition, a single class effect can be

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TABLE 1. Vaughan Williams Classification of Antiarrhythmic Drugs*

	Class I	Class II	Class III	Class IV
	Drugs with direct membrane action (Na channel blockade)	Sympatholytic drugs	Drugs that prolong repolarization	Calcium channel–blocking drugs
Ia:	Depress phase 0 Slow conduction Prolong repolarization			
Ib:	Little effect on phase 0 in normal tissue Depress phase 0 in abnormal fibers Shorten repolarization			
Ic:	Markedly depress phase 0 Markedly slow conduction Slight effect on repolarization			

*This is the classification as modified by Harrison and others.[1-3]

produced by multiple mechanisms. For example, prolongation of action potential duration (i.e., a class III effect) can result from block of any one of a number of K^+ channels or from modification of Na^+ or Ca^{2+} channel function. Moreover, the multiple subdivisions of class I create a problem in placement of drugs based on their effects on conduction and on repolarization. In fact, some drugs have several classes of actions. As an example, amiodarone, the prototype of class III, has class I, class II, and class IV effects, and no one or combination of amiodarone's known effects explains why it is so effective clinically.

2) The classification essentially describes antitachyarrhythmic drugs acting via *block* of channels and currents. The possibility that *activation* of certain channels or receptors might be antiarrhythmic is not considered.

3) The classification is incomplete. For example, α-adrenergic blockers, cholinergic agonists, digitalis, and adenosine are not included. In addition, the potential roles of agents that modulate gap junctional conductance, biochemical pumps, or exchangers are not considered.

4) The classification (excluding class II) is primarily based on the effects of drugs on electrophysiological characteristics of isolated, normal cardiac tissues. However, in diseased tissues, where arrhythmias are likely to arise, channels and receptors are modified, and the actions of drugs may be modified as well.

5) The classification does not incorporate the concept that antiarrhythmic drugs can be effective in various ways: slowing tachycardias and making them better tolerated, terminating established arrhythmias, or preventing arrhythmia initiation.

6) In simplifying matters, the classification suggests we know more than we do. This can have serious consequences when physicians or regulatory agencies assume, without adequate information, that a drug in a given class will have the favorable and/or unfavorable effects characteristic of other drugs assigned to that same class.

These limitations and the increasing complexity of information concerning the pathophysiology of arrhythmias and the clinical efficacy of drugs make it clear that a more sophisticated framework for understanding antiarrhythmic drug actions and their relation to clinical drug efficacy is needed. The goal of this workshop was to reconsider the actions of antiarrhythmic drugs and to develop a rational and useful construct whereby basic and clinical investigators and clinicians might communicate and design research more effectively in order to further drug development, evaluation, and administration.

Approach

We recognized that a classification of antiarrhythmic actions of pharmacological agents might be constructed within various frameworks. For example, drug actions can be expressed at the molecular level (i.e., direct effects on channels and/or receptors). Although our understanding of drug actions at this level is far from complete, it does provide one framework to which new knowledge may be added and from which mechanistic and therapeutic insights and ideas concerning drug development may be gained. Advances in molecular biology and biophysics have identified numerous sites of drug action, both real and potential. For this reason, any workable classification based on specific direct effects would require astute powers of discrimination to select those effects that are physiologically important and those that are artifacts of the experimental system. While an effective classification of drugs should include actions on targets at the molecular level, this inclusion is more useful for basic research rather than clinical directions.

An alternative and very pragmatic framework might classify drugs in terms of their effects on a specific type of arrhythmia in humans. This would have the advantage of allowing a one-step process of drug selection by the clinician. Once a diagnosis is made, a drug might be selected from the group of pharmacological agents whose actions are associated

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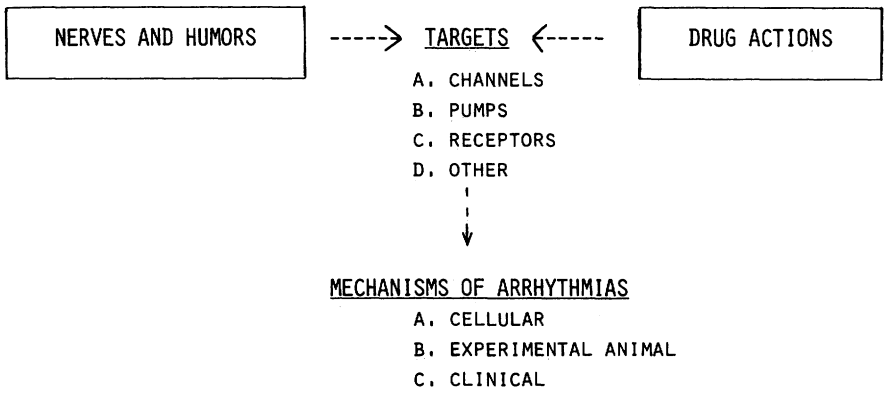

FIGURE 1. *Elements for a classification system. See text for discussion.*

with the arrhythmia diagnosed. However, there are several disadvantages to such a classification. First, if a grouping were created according to site of origin of an arrhythmia, this would result in a large number of diagnostic categories. Second, drug effects vary markedly even for morphologically similar arrhythmias. Susceptibility of a given type of arrhythmia to a drug will be affected by associated factors including (but not limited to) electrolyte balance, ischemia, mechanical factors (stretch), and neural influences. Further, very few, if any, studies are available that would allow an interindividual comparison of drugs in the same setting, and different mechanisms might lead to the same "phenotype" of arrhythmia on the surface electrocardiogram. In summary, no absolute and rigorous classification of drug effects on the basis of clinical efficacy appears possible at present.

Another possibility is that no simple classification is adequate but that a framework could be constructed that incorporates the broad spectrum of knowledge about the actions of drugs, the mechanism(s) of arrhythmias, and the "vulnerable parameters" or targets in the arrhythmia mechanism a drug might modify. Such information might ultimately be linked to the mechanisms underlying clinical arrhythmias since, increasingly, clinical diagnostic categories are expressed in terms of arrhythmia mechanisms (e.g., atrioventricular [AV] nodal reentrant tachycardia).

Such a framework, based on mechanisms for arrhythmias and stressing the interrelations of drugs and their targets, has several advantages. It groups drugs having various actions according to that action that is relevant to countering the arrhythmogenic mechanism. For example, the group of drugs that are clinically effective for AV nodal reentrant tachycardia is representative of three different classes (Ic, II, and IV) in the Vaughan Williams classification but incorporates, as well, several drugs outside that classification (adenosine, cardiac glycosides, and muscarinic agonists). In the proposed classification, these diverse agents might be grouped according to a common action to depress conduction dependent on either Na^+ current or Ca^{2+} current. In addition, such a system could be expanded as understanding of mechanisms or number of drugs is increased.

A classification based on mechanisms for arrhythmias also would encourage the search for clinical information that might clarify the causes of arrhythmias in patients. Even now, suppositions about mechanism are often implicit in drug selection. For example, the selection of an agent to depress conduction or prolong refractoriness in treating ventricular tachycardia is based on the assumption (often unperceived) that the mechanism is reentry. A classification based on mechanisms would require that assumptions underlying current practices be reevaluated through suitable and adequate tests. It would thus require a focus on variables most likely to be suitable for modification by a therapeutic agent. Such a classification also would encourage drug development tightly linked to the evolving understanding of arrhythmogenic mechanisms. It would stimulate the education of students, trainees, clinicians, and scientists about the relations between drug actions and the mechanisms of arrhythmias. Finally, it would interface readily with concepts and knowledge in clinical medicine and in the basic sciences; in fact, the key to the success of such a classification would depend on the extent and the success of its interface with a number of basic and clinical elements. These elements are summarized in Figure 1 and are described in detail in the following pages. Here, we will first provide a description of the *targets* of drug action (i.e., the sites at which drugs act, including channels, pumps, and receptors) and of the effects of drugs at the cellular and molecular levels. We then will consider the effects of drugs in relation to the mechanisms responsible for cardiac arrhythmias in experimental studies. Finally, the application of information about antiarrhythmic drugs to clinical therapy will be reviewed. Incorporated with the above information is a multidimensional classification that we believe describes current knowledge cohesively and provides a convenient framework for interpreting future developments.

Molecular and Cellular Targets of Drug Action

Antiarrhythmic drugs interact with cellular structures that influence electrophysiological function. These structures include ion channels, pumps/carriers,

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receptors, and perhaps some cytoplasmic regulators of second messenger systems. In theory, the actions of drugs can be understood from a combination of the identification of their targets, knowledge of the modification they cause in the function of the target system, and awareness of the role the target system plays in determining electrophysiological behavior.

Our ability to identify drug targets and the nature of drug–target interactions has increased dramatically with the availability of a variety of molecular techniques. We now know the primary molecular structures of many ion channels, pumps, and receptors, and this provides the opportunity to determine drug binding sites. This understanding has greatly increased our insight into the complex interplay of ionic currents that underlies cardiac electrical behavior. The following section identifies the molecular targets for drug action on electrophysiological function and provides a functional definition of the characteristics of drug action on these targets.

Molecular Targets for Drug Action

Channels. Channels are large glycoproteins that span the membrane bilayer and, under an appropriate stimulus, form pores that permit ions to cross the membrane rapidly, thereby creating ion currents. A channel is often selective for certain ions (e.g., sodium channels or potassium channels), although different channels can incorporate regions in which the amino acid sequences are quite similar (homologous). Channel proteins that have similar sequences and physiological properties are termed "isoforms." Some channels only open after a delay following the stimulus, and some channels rectify; that is, they conduct ions more effectively in one direction across the membrane than the other. Stimuli for channel opening include a change in membrane voltage; chemical signals, which may act directly or by occupying an adjacent receptor; or mechanical deformation. It appears likely that these stimuli act by inducing conformational changes in the channel proteins.

The process whereby an ion channel protein responds to an external stimulus to change conformation is termed "gating." Channel activation is similar to (but may not be synonymous with) channel opening. The rate of change of channel conformation (gating kinetics) can be very rapid, with major changes in channel function occurring in less than 1 msec, or quite slow, with changes occurring over seconds. Gating kinetics should not be confused with the kinetics of antiarrhythmic drug binding to or dissociation from channels, which occur at different rates for different drugs. Once open, channel proteins may stay open until closed by another signal, or they may inactivate, that is, close even in the face of a maintained stimulus. Inactivated channels generally do not reopen when restimulated until they have recovered from inactivation, a time- (and often voltage-) dependent process.

Channels can be classified according to the mechanisms that govern their opening: voltage-gated or ligand-gated. A number of channel types have been purified, cloned, and sequenced from heart and from other excitable cells.[4] They share considerable homology, especially in the intramembranous segments, such that it is not surprising that some channel-active drugs interact with more than one channel type. In addition, channels of one type (e.g., the sodium channels) are even more homologous among tissues, so that drugs that interact with one channel type in heart may also interact with that channel type in the nervous system. The progress in determining channel structure encourages us to believe that it will soon be possible to determine key structural differences and drug binding sites and to tailor drugs that are tissue- and channel-specific. A schematic representation of the role of channels and pumps/carriers in generating the normal transmembrane resting and action potentials is illustrated in Figure 2. Knowledge of the structure and function of channels and pumps/carriers is increasing rapidly, and the following tabulation will thus require a regular update.

CHANNELS THAT CARRY INWARD CURRENTS: SODIUM CHANNELS. These channels represent a family of large proteins with multiple subunits.[4] The main (α-) subunit contains about 2,000 amino acids and includes four major repeated internal sequences that represent internal subunits. Presently, five members of this family have been cloned and expressed, including one from heart muscle. In brain and skeletal muscle, the α-subunit is normally accompanied by other subunits, but it is functional even when alone. The α-subunit in heart is also functional alone,[5] although some evidence suggests that there may be an additional subunit. Functional evidence points to at least two isoforms of the cardiac sodium channel.

I_{Na} is the inward excitatory current carried by Na^+ through a voltage-activated sodium channel. The current is activated at threshold to produce rapid depolarization and to provide the current to drive action potential or impulse propagation in atrial, His-Purkinje, and ventricular cells. These Na^+ channels are sparse or absent in sinoatrial (SA) and AV nodal cells.[6]

$I_{Na\text{-}B}$ is a proposed background Na^+ current through a voltage-independent channel in SA nodal cells.[7] It is offset by an outward K^+ current at the beginning of phase 4, but as the K^+ current decays, it contributes to pacemaker behavior.

CHANNELS THAT CARRY INWARD CURRENTS: Ca^{2+} CHANNELS. These channels also represent a family of proteins with multiple subunits. Some of the subunits from various tissues, including a cardiac subunit of the L type, have been cloned and sequenced, and they show extensive homology. There are at least two types of calcium channels in the heart.[8] The L type ($I_{Ca\text{-}L}$), which is blocked by verapamil, diltiazem, and the dihydropyridines, predominates in all cardiac tissues studied. The T type ($I_{Ca\text{-}T}$) has been identified in pacemaker tissues. Ca^{2+} channels are also found in high density in vascular smooth muscle, endocrine cells, and the brain.

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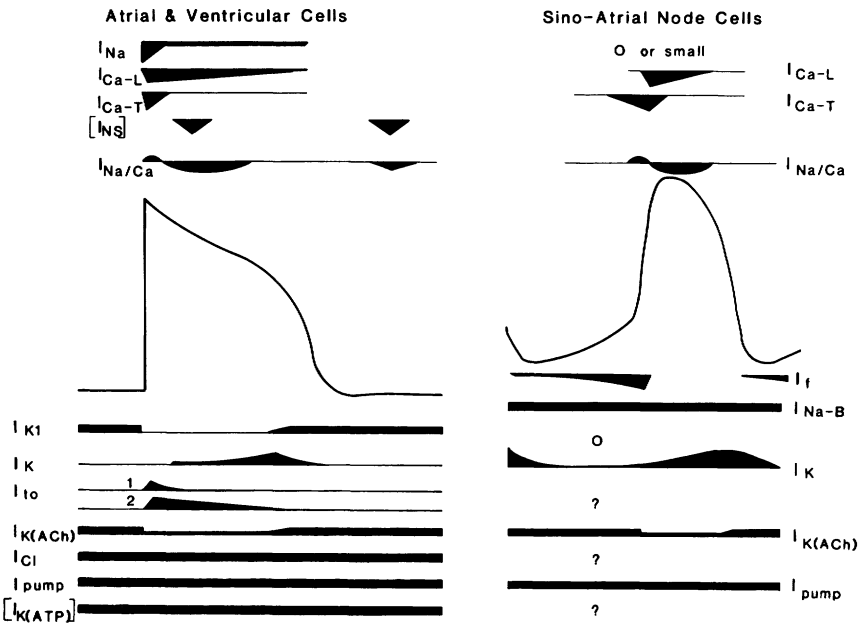

FIGURE 2. *Currents and channels involved in generating the resting and action potential. The time course of a stylized action potential of atrial and ventricular cells is shown on the left and of sinoatrial node cells on the right. Above and below are the various channels and pumps that contribute the currents underlying the electrical events. See text for identification of the symbols and description of the channels or currents. Where possible, the approximate time courses of the currents associated with the channels or pumps are shown symbolically without effort to represent their magnitudes relative to each other. The heavy bars for I_{Cl}, I_{pump}, and $I_{K(ATP)}$ only indicate the presence of these channels or pump, without implying magnitude of currents, since that would vary with physiological and pathophysiological conditions. The channels identified by brackets [I_{NS} and $I_{K(ATP)}$] imply that they are active only under pathological conditions. For the sinoatrial node cells, I_{Na} and I_{K1} are small or absent. Question marks indicate that experimental evidence is not yet available to determine the presence of these channels in sinoatrial cell membranes. Although it is likely that other ionic current mechanisms exist, they are not shown here because their roles in electrogenesis are not sufficiently well defined.*

$I_{Ca\text{-}L}$ is the calcium current that is activated regeneratively from a relatively depolarized threshold potential to produce depolarization and propagation in SA and AV nodal cells. It is also present in atrial, His-Purkinje, and ventricular cells, where it contributes to the plateau and triggers calcium release from the sarcoplasmic reticulum. It is inactivated by both depolarization and $[Ca^{2+}]_i$, but it usually lasts long enough to contribute to the overall plateau currents. It is the target for the clinically useful calcium channel blockers, and it is strongly modulated by neurotransmitters.[8]

$I_{Ca\text{-}T}$ is a calcium current through a different voltage-gated channel that is activated at potentials intermediate between thresholds for I_{Na} and $I_{Ca\text{-}L}$. It probably contributes inward current to the later stages of phase 4 depolarization in SA node and His-Purkinje cells, and it may also play a role in abnormal automaticity in atria.[7] It is almost absent from ventricular cells.

OTHER INWARD CURRENT CHANNELS. There are two cationic nonselective channels that under normal physiological conditions allow current to be carried by Na^+. They are not well characterized, and no structural information is available yet.

I_f is an inward current carried by Na^+ through a relatively nonspecific cationic channel that is activated by polarization to high membrane potentials in SA and AV nodal cells and His-Purkinje cells.[9] This current generates phase 4 depolarization and contributes to pacemaker function. Its kinetics are fairly slow, and it is strongly modulated by neurotransmitters.

I_{NS} is a channel that is gated by $[Ca^{2+}]_i$.[10] It is a cationic nonselective channel that if activated at the resting potential, produces an inward current carried by Na^+. Under some conditions, it is activated by Ca^{2+} release from the sarcoplasmic reticulum during $[Ca^{2+}]_i$ overload and contributes to delayed afterdepolarizations (see below).

CHANNELS THAT CARRY OUTWARD CURRENTS. Many functionally different types of potassium channels have been identified in heart and other tissues. Indeed, almost all cells have some type of potassium channel. These channels are composed of four subunits, each about one quarter the size of the sodium channel subunit.[4] It seems likely that naturally occurring potassium channels are composed of different subunit types. It has not yet been possible to match the cloned channels with the functional currents, so this discussion will focus on K^+ currents defined functionally.

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I_{K1} is the K^+ current responsible for maintaining the resting potential near the K^+ equilibrium potential in atrial, AV nodal, His-Purkinje, and ventricular cells.[11] This current, which is also called the "inward rectifier," shuts off during depolarization (inward rectification). Its absence from SA node cells is important in letting small currents control the pacemaker rate.

I_K is a K^+ current carried through voltage-gated channels with slow activation kinetics, giving it the name "delayed rectifier." I_K turns on slowly during the action potential plateau and is the major current causing repolarization. After repolarization it turns off slowly enough in the SA node to contribute to phase 4 depolarization. There are probably several pharmacologically different I_K channels, a subset of which can be modulated by neurotransmitters.[12,13]

I_{to} is a K^+ current that turns on rapidly after depolarization and then inactivates. One type of I_{to} is activated by $[Ca^{2+}]_i$, and the other is voltage-activated and modulated by neurotransmitters.[14] I_{to} can play an important role in modifying action potential duration and in contributing to the heterogeneity of repolarization because of its nonuniform distribution (it is present in subepicardial but not subendocardial muscle). Similar currents, called I_A, are found in nerve and skeletal muscle cells.

$I_{K(ACh)}$ is a K^+ current whose channel is activated by the muscarinic (M_2) receptor via GTP regulatory (G) protein signal transduction.[15] It shuts down somewhat during depolarization (inward rectification), but it contributes outward current both at rest and during the action potential. It is particularly important in the SA and AV nodes and in atrial cells, where it can produce substantial hyperpolarization, and in atrium, where it produces marked acceleration of repolarization. This channel also is opened by activation of the purinergic (adenosine) receptor and so the current also is designated $I_{K(Ado)}$.

$I_{K(ATP)}$ is a K^+ current carried through a metabolically regulated channel.[16] This channel is blocked by ATP and is strongly activated during hypoxia. The channel has been present in all cardiac cells studied, but it has not been identified in the SA node. It may contribute to shortening of the action potential during ischemia. Experimentally available antiarrhythmic drugs can either increase or decrease this K^+ current, thereby accelerating or prolonging repolarization.

I_{Cl} is a Cl^- current, usually quite small, but which can be greatly increased by adrenergic receptor activation, favoring repolarization.[17] Because the Cl^- concentration is sometimes above what is expected for equilibrium, the Cl^- channel could under those circumstances generate inward current. Because the channel rectifies, the inward current could be quite small, but it might contribute to pacemaker depolarization.

$I_{K(Ca)}$ is a K^+ current carried through a channel that is activated by $[Ca^{2+}]_i$. It appears to require very high levels of $[Ca^{2+}]_i$ for activation. Its presence in cardiac cells has been hard to establish, and its physiological role is not yet clear.[11]

SOME OTHER IMPORTANT CHANNELS. Cardiac cells are coupled electrically and chemically to one another by large channels called gap junctions or connexons.[18] These junctions are composed of two multimeric complexes, one set for each cell. The two sets align themselves to form a large pore between the cells that permits passage of ions and small molecules. The conductance of gap junctions is regulated by $[Ca^{2+}]_i$ and pH_i and perhaps by phosphorylation via activation of the β-adrenergic receptor system. They play a major role in isolating cells damaged by ischemic injury or trauma from adjacent more normal cells.

A calcium channel in the sarcoplasmic reticulum can be triggered to release Ca^{2+} by calcium entry through $I_{Ca\text{-}L}$. Because it also can be modulated by the drug ryanodine, it is often called the ryanodine receptor.[19]

Pumps/carriers. ACTIVE TRANSPORT. At least two ATP-dependent pumps in the sarcolemma generate ionic current, the Na-K pump (which is blocked by digitalis) and the calcium pump. Several isoforms of the Na-K pump have been identified by differing affinities for digitalis. A different ATP-dependent calcium pump is found in the sarcoplasmic reticulum. Both sarcolemmal pumps have been cloned and sequenced, and several isoforms of the Na-K pump are identified. Some evidence suggests that they are modulated by phosphorylation through the adrenergic receptor system. $I_{Na\text{-}K\ pump}$ is the current generated by the Na-K pump. Because each cycle transports three Na^+ out and two K^+ into the cell, it generates a small outward current that is relatively constant during the cardiac cycle.[20]

CARRIERS. This group of membrane proteins facilitates exchange of ions or substrates, or pumps them using energy. It includes the Na/Ca countertransport system in the sarcolemma and in the mitochondria, the Na/H exchanger, the Na/K/Cl cotransporter, and the Cl/HCO_3 exchanger. The cardiac Na/Ca exchanger has recently been cloned, but no selective blocking or activating drugs are presently known. Amiloride blocks the Na/K/Cl cotransporter and the Na/H exchanger, as well as several types of channels.

$I_{Na/Ca}$ is the current generated by the Na/Ca countertransport system, which exchanges 1 Ca^{2+} for 3 Na^+.[21] It is the chief means of Ca^{2+} efflux through the sarcolemma. The direction of the current depends on the relation between the Na^+ and Ca^{2+} gradients and the membrane potential. At the resting potential the exchanger generates a small inward current, but upon depolarization the current may show a brief outward phase and then become inward as $[Ca^{2+}]_i$ rises. During $[Ca^{2+}]_i$ overload, the sarcoplasmic reticulum may release Ca^{2+} spontaneously during diastole, causing the Na/Ca exchanger to generate a larger inward current, and thereby contributing to the generation of delayed afterdepolarizations (see below).

Receptors. The autonomic nervous system is an important modulator of cardiac rhythms. α- and

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β-adrenergic, muscarinic and purinergic receptors influence various channels and pumps, which, in turn, influence the initiation and propagation of normal and abnormal cardiac impulses. The receptor systems in the heart are coupled by G proteins to their effector systems.[22] These G proteins translate the results of an external stimulus, such as receptor occupancy, into a physiological response, such as activation of a kinase and subsequent phosphorylation of target proteins (e.g., ion channels). Alternatively, they may link receptors to second messenger systems and pumps. The two best understood receptor-effector coupling systems are the β_1-adrenergic and the M_2 muscarinic.

β-ADRENERGIC RECEPTOR–EFFECTOR COUPLING SYSTEM. Both β_1- and β_2-adrenergic receptors exist in the hearts of various species, including humans,[23] but the contribution of the β_2 component is not yet clear. Both receptor subtypes are coupled to adenylate cyclase via the G protein G_s. β-Adrenergic receptor stimulation modulates L-type calcium channels, the I_f channel, various potassium channels, I_{Cl} and, under certain conditions, sodium channels.

The binding of agonist to β-adrenergic receptor in cardiac myocytes increases intracellular cyclic AMP levels, activating the cyclic AMP-dependent protein kinase and phosphorylating a peptide associated with the L-type Ca^{2+} channel, increasing Ca^{2+} current and contractility.[24] The chronotropic effect of β-adrenergic stimulation is also mediated by an increase in cyclic AMP that appears to shift the activation curve of the pacemaker current I_f toward more positive potentials.[25] β-Adrenergic stimulation also enhances Na-K pump function, which would tend to hyperpolarize cardiac fibers, especially those that are partially depolarized as in the setting of acute ischemia.

A fast, direct G protein (G_s) coupling between β-adrenoceptors and calcium, I_f, and sodium channels has recently been documented.[26] I_K and a component of I_{to} are enhanced by β-adrenergic stimulation,[27] whereas I_{K1} does not appear to be affected.[10] β-Adrenergic stimulation enhances voltage-dependent K^+ and voltage-independent Cl^- currents.[28]

There appear to be physiological and pathophysiological importance of each of these actions, as follows: The effect on the L-type Ca^{2+} channel could, in its own right, induce early afterdepolarizations and triggered activity, as well as increase free intracellular Ca^{2+} concentrations, which in turn would potentiate delayed afterdepolarizations and resultant triggered activity. The effect on I_f can increase the rate of impulse initiation of the sinus node pacemaker, as well as of latent atrial and ventricular pacemakers. The potassium channel effects tend to accelerate repolarization and shorten refractoriness, and both the Ca^{2+} and K^+ channel effects may combine to accelerate AV nodal conduction and shorten AV nodal refractoriness. These ion channel effects can account for the tachycardias and QT interval shortening associated with sympathetic stimulation of the intact heart.

Clinically, β-adrenergic blocking agents have well-established effects on those arrhythmias that require the participation of the AV node. The β-adrenergic blocking effects result largely from drug-induced decreases in conduction velocity and prolongation of refractoriness in the AV node, actions reflecting block of catecholamine effects on Ca^{2+} and K^+ channels. Limited subsets of patients with various ventricular arrhythmias, for example, some ventricular premature depolarizations, exercise-induced ventricular tachycardias, some ventricular tachycardias inducible by programmed stimulation, and adenosine sensitive ventricular tachycardias, also may respond to β-adrenergic blockade. β-Adrenergic blocking drugs also reduce the risk of sudden cardiac death in selected population subgroups (e.g., post–myocardial infarction, long QT syndrome). In post–myocardial infarction patients, the mechanisms of protection are not yet fully understood.

α-ADRENERGIC RECEPTOR–EFFECTOR COUPLING SYSTEM. There are two and possibly three α_1-adrenergic receptor subtypes in the heart,[29] linked via G proteins to a series of effector processes (Na-K pump,[30] K channels,[31] and phospholipase C[29]) that modulate impulse initiation and repolarization. Information on second messenger involvement in these processes is incomplete. The Na-K pump-stimulating effect is responsible for a decrease in the rate of impulse initiation by automatic fibers outside the sinus node, and the decreases induced in I_{K1} and/or I_{to} result in prolongation of repolarization.[30,32]

Studies in isolated tissues suggest that α_1-adrenergic receptor subtype stimulation also can be arrhythmogenic. α_1-Agonists induce triggered rhythms via delayed or early afterdepolarizations and abnormal automatic rhythms[33,34] studied in settings where $[Ca^{2+}]_o$ is elevated, repolarization is prolonged, ischemia and reperfusion are simulated, or infarction is induced. In intact cats after coronary occlusion and reperfusion, there is an increase in α_1-adrenergic receptor number and affinity.[35] This is associated with ventricular tachycardia and fibrillation that start occasionally during ischemia and invariably within 1–3 minutes of reperfusion.

For humans, only limited data are available concerning α-adrenergic involvement in cardiac arrhythmias. The efficacy of phentolamine against arrhythmias in a small group of patients in the immediate postmyocardial infarction period has been reported. In patients with the congenital long QT syndrome, a subset whose arrhythmias are not blocked by propranolol do respond to left thoracic sympathectomy, leading to the speculation that α-adrenergic mechanisms may be involved.[36] In summary, the clinical antiarrhythmic potential of α-adrenergic blockade remains largely untested.

MUSCARINIC RECEPTOR–EFFECTOR COUPLING SYSTEM. The M_2 receptor has been identified pharmacologically as the dominant cardiac muscarinic receptor.[37] Its density is two to five times higher in the atria than the ventricles.[38] The M_2 receptor is coupled

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directly to the ligand-operated potassium channel [$I_{K(ACh)}$] by the G protein G_K.[39] The M_2 receptor also inhibits adenylate cyclase via G_i and in this way affects currents that are modulated by the cyclic AMP dependent protein kinase, including $I_{Ca\text{-}L}$, I_f, and presumably I_K.[40]

A major aspect of muscarinic action on the heart is the antagonism of adrenergic effects at the level of the adenylate cyclase–cyclic AMP system.[40] Whereas β-adrenergic agonists stimulate the cAMP second messenger system via the G protein G_s, muscarinic agonists such as acetylcholine inhibit this same system via G_i.[39] The effects of muscarinic activation on Ca^{2+} and K^+ currents contribute to the depression of conduction in the AV node. The effects of M_2 agonists to decrease I_f and to increase conductance of the muscarinic K^+ channel suppress the sinus node pacemaker.[4] M_2-receptor activation leads to an increase in $I_{K(ACh)}$, which hyperpolarizes and shortens the action potential in atrial tissues.[41]

Increased vagal activity (whether due to direct stimulation or to pharmacological activation) reduces the incidence of ventricular fibrillation during acute myocardial ischemia in intact animals.[42] This effect is only in part dependent on heart rate reduction; it also depends on the antiadrenergic action of muscarinic activation. Muscarinic blockade with atropine sometimes increases the incidence of ventricular fibrillation during ischemia.

Clinically, vagal activation is effective against arrhythmias involving the AV node. There is no direct evidence for an antiarrhythmic effect of vagal activation at the ventricular level in human subjects. There is indirect evidence that impairment of or a decrease in either vagal tone (heart rate variability)[43] or reflexes (baroreflex sensitivity)[44] is associated with increased mortality and incidence of sudden death among post–myocardial infarction patients. Hence, there is direct evidence that an antiarrhythmic action of muscarinic agonists occurs at the supraventricular level and indirect evidence suggesting that an important role may be played in ventricular arrhythmias and sudden death.

PURINERGIC RECEPTOR–EFFECTOR COUPLING SYSTEM. The cardiac purinergic receptor population is designated A_1. It is coupled presumably by G_K to the ligand-operated potassium channel [$I_{K(Ado)}$].[45] As such, its actions are thought to reflect operation of the same effector coupling pathway as that described for the M_2 muscarinic receptor. Clinically, a subset of benign ventricular tachycardias is terminated by the α_1-agonist, adenosine. Of greater importance, reentrant tachycardias involving the atrioventricular node are consistently terminated by adenosine.[46] Hence, this receptor-effector system offers an attractive target for therapeutic interventions.

Cytoplasmic regulators of second messengers. We are becoming increasingly aware of the roles a variety of molecules may play in the regulation of second messengers. The latter, in turn, exert important influences on ionic currents. For example, agents that block cyclic AMP–phosphodiesterase may increase cyclic AMP and affect target channels such as the L-type calcium channel. Receptors for angiotensin and α_1-adrenoreceptors activate phospholipase C, which in turn activates protein kinase C via diacylglycerol and releases inositol trisphosphate. The diacylglycerol–protein kinase C pathway results in phosphorylation of transsarcolemmal Ca^{2+} channels, and the inositol trisphosphate pathway induces sarcoplasmic reticulum release of Ca^{2+}. Both events would increase free intracellular Ca^{2+}. Other examples of regulators are: phospholipase A_2 may stimulate the ligand-activated $K_{(ACh)}$ channel via arachidonic acid metabolic pathways; long-chain fatty acids[18–20] are reported to activate delayed rectifier K currents; and finally, dephosphorylation is promoted by phosphatases and a specific muscle phosphatase inhibitor, okadaic acid, is known to increase cardiac calcium currents.

Functional Definition of Drug Action

Although characterization of a drug's action on its target channel, pump, or receptor is an effective way to determine its molecular site of action, studies of drug effects on function are crucial to an understanding of the complex interactions between drugs and the heart. These studies at the cellular, tissue, or intact organism level can be performed using a variety of experimental and clinical indexes, as reviewed in this section and Table 2.

Pharmacodynamics. A variety of experimental variables can be used to study pharmacodynamics, as listed in Table 2. Those variables modified by drug action include the ionic currents that flow through channels, the activities (i.e., free concentrations) of ions intracellularly and extracellularly, the transmembrane action potential characteristics of single cells or intact tissues measured using microelectrodes; surface electrogram measurements of electrical activity in tissues; and the properties of excitability, conduction, refractoriness, and impulse initiation.

Drug-channel interactions. A major determinant of the effects of antiarrhythmic drugs is seen in their actions at their channel binding sites. It must be understood that the drug binding sites in channels are thought to reside at specific loci, the access to which is determined by molecules or "gates" that may be opened or closed depending on time- and/or voltage-regulated processes. The channels themselves may be construed of as residing in resting states, where ionic current is not being passed; in open states, where ions can pass; and in inactivated states, where ions are no longer being carried and a transition back to the resting state is occurring. Whereas most channel-active agents act to block ionic currents, a few [e.g., activators of $I_{K(ATP)}$] can modify electrophysiological behavior by increasing current.[47–50]

Most antiarrhythmic drugs behave as though they do not have continuous access to their binding sites. As a result, their intermittent blocking action de-

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TABLE 2. Pharmacological Indices Associated With the Functional Definition of Drug Action

Experimental variables used to study pharmacodynamics
Ionic currents
Ionic activity
Transmembrane action potential
Extracellular electrogram
Excitability
Conduction
Refractoriness
Impulse initiation
Pharmacodynamics
Drug-channel interactions
Tonic block
Phasic block
Use dependence
Voltage dependence
Recovery from phasic block
Voltage dependence
Competition and interaction
Ions
Drugs
Receptor-mediated modulation
Nonelectrophysiological properties
Cardiac contractility
Vascular tone
Cardiac disease
Pharmacokinetics
Bioavailability
Absorption
Distribution
Clearance
Metabolites

pends not only on the drug concentrations but also on the variables that influence association with and dissociation from their binding sites on the protein.[47–52] Local anesthetic antiarrhythmic drugs that have continuous access to binding sites on the channel will demonstrate tonic block, that is, block that develops in the absence of excitation.[47,49] This can be assessed by measuring the degree of reduction in ionic current that is present with infrequent stimulation. In general, the degree of tonic block correlates with the degree of lipid solubility.[49,52]

When heart rate or rate of stimulation of isolated tissues is increased, most local anesthetic antiarrhythmic drugs induce an additional reduction of sodium current, that is, phasic block.[47–52] Phasic block is generally attributed to intermittent access to or variable affinity for channel binding sites that depends on the gating state of the channel.[53,54] Most antiarrhythmic drugs have relatively low affinity for sodium channels in the resting state, and the affinity increases as the channel activates.[49–55] Furthermore, drug affinity for the different activated or inactivated states may vary, so that association of the drug with the channel can occur preferentially during channel activation to the open state (i.e., just before or during the upstroke of the action potential) or during the prolonged plateau period when the channel is inactivated.[49–55] In this way, use dependence of phasic block may depend on the duration of the action potential as well as the number of activations occurring.

The magnitude of use dependence is also voltage dependent.[56] This reflects the fraction of sodium channels that activate in response to a depolarizing pulse and become accessible to the blocking action of the drug as well as the direct effects of voltage on the ionized form of the drug. Voltage dependence assumes particular importance in pathophysiological settings such as ischemia, which reduce the membrane potential of cardiac cells. Drugs such as lidocaine show voltage dependence, having a far greater effect on conduction in depolarized than in normally polarized tissues.

Because phasic block represents the balance between drug association with and dissociation from its binding site, measurement of recovery from block also has been helpful in elucidating drug–channel interactions, as recovery is believed primarily to reflect dissociation.[47,49,52] Recovery from block can either be directly or inversely dependent on voltage or independent of voltage.

Many antiarrhythmic drugs prolong repolarization, an effect that is usually mediated by their actions on potassium channels.[57,58] It is of interest that most antiarrhythmic drugs that alter repolarization do so in such a way that prolongation of repolarization is greatest at the slowest heart or stimulation rates and progressively decreases as the rate of stimulation increases. This phenomenon is described as "reverse use dependence." This has been attributed to a reduction in potassium channel blockade during the plateau or at positive potentials such that block decreases as use increases.

Because refractoriness is determined by the availability of sodium channels to respond to excitation as well as by other determinants of excitability, changes in repolarization as well as residual sodium channel block present during phases 3 and 4 of the transmembrane action potential will determine a drug's effects on refractoriness. Given the complicated interplay between stimulus rate and ion channel blockade, drug effects on refractoriness will be rate dependent. The magnitude of this rate dependence will vary for different drugs.[49,57,58]

Drug competition and interaction. Some drugs interfere with each other by directly competing for the same receptor or by producing offsetting electrophysiological effects.[59,60] Others can enhance each other's efficacy either by summating physiological effects, thereby allowing the administration of lower doses of both drugs and reducing the toxicity of both, or by achieving the kinetic mix of on-rate and off-rate that

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best achieves "therapeutic" use dependence. In general, antiarrhythmic drug combinations have not been studied systematically, although such a study represents an opportunity to improve patient management. Even less is known about interactions between the parent drugs and their metabolites, although examples of antagonism have been demonstrated.

Modulation. Little is known at present about the effects of receptor-mediated modulation of channel behavior or drug interaction, but any alteration in membrane potential or temporal distribution of channel state (as described under "Receptors") would be expected to affect drug action.

Effects of nonelectrophysiological properties. Drugs that block the calcium or sodium channel can also have substantial negative inotropic effects, curtailing their usefulness in clinical conditions associated with depressed cardiac contractile function. Adrenergic receptor modulation may also affect contraction. Similarly, changes in vascular tone consequent to direct drug action on the vasculature have potentially important effects on heart rate and metabolic state. Finally, disease states themselves may alter channel properties as well as the actions of receptors or pumps, further modifying drug action.

Pharmacokinetics. A complete drug evaluation requires definition not only of its pharmacodynamics but its pharmacokinetics as well. Important considerations are kinetics of absorption, distribution, and clearance (elimination and inactivation); formation of metabolites and their actions; relative potency of stereoisomers when the drug is a racemic mixture; and pharmacogenetic defects in metabolism. Often, metabolites have major therapeutic or toxic effects. Stereoisomers may have different rates of elimination and differing, and sometimes opposing, actions. Distribution of drugs into the brain (via the blood–brain barrier) or other tissues can contribute to toxicity. Direct or indirect interaction with other drugs may influence a drug's effective blood level or therapeutic usefulness. Target specificity plays an important role here, as well. As discussed earlier, many antiarrhythmic drugs have more than one target, rendering these actions and interactions exceedingly complex.

Arrhythmogenic Mechanisms in the Cell and the Heart

Arrhythmogenic Mechanisms and the Concept of the "Vulnerable Parameter"

Thus far, we have reviewed the potential targets of drug action and placed them in a framework wherein the mechanisms of drug action might begin to be considered at the cellular level. In this section, we consider the arrhythmia mechanisms themselves and develop the framework for classification of drugs. The arrhythmogenic mechanisms selected to provide the basis for classification are those most commonly associated with clinically important tachyarrhythmias.

We assume that for each arrhythmogenic mechanism an alteration in one or more of several electrophysiological properties will be sufficient to terminate the arrhythmia or to prevent its initiation. In addition, we assume that among the several possible effective changes in electrophysiological properties, usually one is most susceptible to alterations while manifesting a minimum of undesirable effects on the heart. It is this property that we characterize by the term "vulnerable parameter." In the following section, we briefly describe the various arrhythmogenic mechanisms and identify their most likely vulnerable parameters. The mechanisms and vulnerable parameters are summarized at the cellular electrophysiological level in Table 3 and for the intact heart in Table 4.

Enhanced normal automaticity. Automaticity is the property of spontaneous impulse initiation by cardiac fibers. This results from depolarization during phase 4, secondary to an inward current carried by Na^+ and designated I_f[9] (Figure 2). The slow depolarization during phase 4 can be enhanced by various factors, such as adrenergic stimulation of either the normal sinus node pacemaker or subsidiary pacemakers in specialized tissues, which may then usurp control of cardiac rhythm. Modification of the rate of an enhanced normally automatic focus can result from interventions that change, singly or in concert, the maximum diastolic potential, the rate of phase 4 depolarization, the voltage of the threshold potential, or action potential duration.[60]

The complexity of the relations among these variables is seen in the fact that a change in one is likely to change some of the others. For example, an increase in K^+ currents will hyperpolarize the membrane (which in itself will slow the automatic rate). However, increasing K^+ currents also will shorten the action potential duration and activate I_f sooner, and both changes will increase the rate. Further, increasing outward K^+ currents may counteract the inward pacemaker current, thereby decreasing rate. Hence, the ultimate expression of pacemaker rate reflects a balance achieved among a number of interacting factors, no one of which is of paramount importance.[61] Arrhythmias caused by enhanced normal automaticity that may need treatment are inappropriate sinus and atrial tachycardias and some accelerated idioventricular rhythms. For such arrhythmias caused by enhanced normal automaticity, the vulnerable parameter is phase 4 depolarization.

Abnormal automaticity. Abnormal automaticity is the mechanism by which spontaneous impulses are generated in fibers that are partially depolarized because of some pathological process. Atrial and ventricular muscle can become automatic by this mechanism, which also may change the basis for automatic firing in specialized fibers other than those of the sinus node. The characteristics of abnormal automaticity, judged from experimental studies, are a function of the magnitude of the membrane depolarization.[62] As described above, at high levels of membrane potential in the Purkinje system, the pacemaker current is I_f, an inward Na^+ current. If maximum diastolic potential is reduced to −75 to

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TABLE 3. Classification of Arrhythmogenic Mechanisms at the Cellular Level in Terms of Vulnerable Parameters

Mechanism of arrhythmia	Vulnerable parameter (antiarrhythmic effect)	Ionic currents most likely to modulate vulnerable parameter
Automaticity		
Enhanced normal automaticity	Phase 4 depolarization (decrease)	I_f; $I_{Ca\text{-}T}$ (block) $I_{K(ACh)}$ (activate)
Abnormal automaticity	Maximum diastolic potential (hyperpolarize) or Phase 4 depolarization (decrease)	I_K; $I_{K(ACh)}$ (activate) $I_{Ca\text{-}L}$; I_{Na} (block)
Triggered activity based on		
Early afterdepolarizations (EAD)	Action potential duration (shorten) or EAD (suppress)	I_K (activate) $I_{Ca\text{-}L}$; I_{Na} (block)
Delayed afterdepolarizations (DAD)	Calcium overload (unload) or DAD (suppress)	$I_{Ca\text{-}L}$ (block) $I_{Ca\text{-}L}$; I_{Na} (block)
Reentry dependent on sodium channels		
Primary impaired conduction (long excitable gap)	Excitability and conduction (decrease)	I_{Na} (block)
Conduction encroaching on refractoriness (short excitable gap)	Effective refractory period (prolong)	I_K (block)
Reentry dependent on calcium channels	Excitability and conduction (decrease)	$I_{Ca\text{-}L}$ (block)
Other mechanisms		
Reflection	Excitability (decrease)	I_{Na}; $I_{Ca\text{-}L}$ (block)
Parasystole	Phase 4 depolarization (decrease)	I_f (block) (if maximum diastolic potential high)

−70 mV, as might occur in the setting of mild ischemia, I_f could still provide some of the phase 4 depolarizing current, and the upstrokes of the action potentials generated by the abnormally automatic cells would depend largely on sodium entry. If, on the other hand, maximum diastolic potential is reduced to −50 to −55 mV (as the result of a greater degree of ischemia), the depolarization during phase 4 would not be caused by I_f but rather by the decay of repolarizing K^+ currents, and the action potentials generated, like those of the sinus node, would depend primarily on I_{Ca}.[63,64] Examples of arrhythmias probably caused by abnormal automaticity are certain ectopic atrial tachycardias[65–68] and accelerated idioventricular rhythms and ventricular tachycardias 24–72 hours after experimental myocardial infarction[69–71] or during the first few days after clinical myocardial infarction.[72,73] In these cases, the most attractive vulnerable parameter is the primary abnormality, that is, the reduced maximum diastolic potential or resting potential, which may respond to K^+ channel activation [e.g., $I_{K(ACh)}$ in atrial cells] or to Na^+-K^+ pump stimulation. However, from a practical point of view, an additional vulnerable parameter is phase 4 depolarization itself.

Triggered activity. Triggered activity refers to a family of arrhythmias that arise as a consequence of afterdepolarizations.[74] The occurrence of an afterdepolarization depends on the prior impulse (or series of impulses). The same relation holds for triggered rhythms induced by afterdepolarizations, in which the triggered action potentials depend on preceding events for their initiation. Afterdepolarizations can either interrupt the process of repolarization or occur after completion of repolarization and are designated respectively as early (EAD) or delayed (DAD) afterdepolarizations (Figure 3).

EARLY AFTERDEPOLARIZATIONS. There are several mechanisms for EADs. All result in a change in net membrane inward current that delays or interrupts repolarization. The primary mechanism may be a reduction in the normal repolarizing current, I_K, an abnormal prolongation of inward current carried by sodium or calcium channels, or the simultaneous operation of enhanced inward and reduced outward current (Figure 2).[74–76]

Depending on the level of the transmembrane potential at which a response is triggered, the upstroke of that response results primarily from inward sodium or calcium current. Parenthetically, if an EAD triggers a series of repetitive responses at a sufficiently positive membrane potential, the mechanisms may be indistinguishable from abnormal automaticity.[77] EAD most often arise at slow heart or stimulation rates or after long pauses in the presence of interventions that prolong the action potential such as decreased extracellular K^+ concentrations or drugs that block I_K or I_{K1}. Studies in experimental animals indicate that EAD can induce torsade de pointes,[78] and some clinical data support this view.[79] EAD may also play a role in reperfusion arrhythmias.[80]

The vulnerable parameter for EAD-related triggered activity is the prolonged action potential duration, and the most rational approach is to shorten the

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TABLE 4. Classification of Drug Actions on Arrhythmias Based on Modification of Vulnerable Parameter

Arrhythmia	Mechanisms	Vulnerable parameter	Representative drugs
	Automaticity		
	Enhanced normal		
Inappropriate sinus tachycardia		Phase 4 depolarization (decrease)	β-Adrenergic blocking agents
Some idiopathic ventricular tachycardias			Sodium channel blocking agents
	Abnormal		
Ectopic atrial tachycardia		Maximum diastolic potential (hyperpolarization) or	M_2 agonists
		Phase 4 depolarization (decrease)	Calcium or sodium channel blocking agents M_2 agonists
Accelerated idioventricular rhythms		Phase 4 depolarization (decrease)	Calcium or sodium channel blocking agents
	Triggered Activity		
	EAD		
Torsade de pointes		Action potential duration (shorten) or EAD (suppress)	β-Agonists; vagolytic agents (increase rate) Calcium channel blocking agents; Mg^{2+}; β-adrenergic blockers
	DAD		
Digitalis-induced arrhythmias		Calcium overload (unload) or DAD (suppress)	Calcium channel blocking agents Sodium channel blocking agents
Certain autonomically mediated ventricular tachycardias		Calcium overload (unload) or DAD (suppress)	β-Adrenergic blocking agents Calcium channel blocking agents, adenosine

action potential (accomplished by increasing heart rate, increasing extracellular K^+ concentration, use of action potential shortening drugs, β-adrenergic activation, and/or withdrawal of the offending drugs) or to use maneuvers that suppress the triggering inward currents. Suppression of triggering inward currents may be effected with drugs that block calcium and sodium currents, drugs that block β- or α-adrenergic receptors, and Mg^{2+}.

DELAYED AFTERDEPOLARIZATIONS. DAD are caused by intracellular calcium overload that results in repetitive release of calcium from the sarcoplasmic reticulum.[74] The resulting oscillatory changes in intracellular calcium activity cause an inward, depolarizing current that underlies the DAD.[74,81] It is uncertain whether the inward current is carried by the calcium-activated nonspecific cation channel (I_{NS}) and/or by the sarcolemmal Na/Ca exchanger.[82,83]

Arrhythmias likely to be DAD-mediated include extrasystoles and tachycardias related to digitalis excess,[84–86] certain catecholamine-dependent atrial and ventricular tachycardias,[87,88] and perhaps some arrhythmias caused by ischemia and reperfusion.[89] The vulnerable parameter is calcium overload, and therefore, DAD-mediated arrhythmias can be countered by any of various means to reduce intracellular calcium (e.g., calcium channel blockade). In addition, drugs may suppress DAD by blocking inward Na^+ current carried by I_{NS} or by increasing potassium conductance and thereby increasing outward current.[90,91]

Reentry. Reentrant excitation can result from circus movement or reflection. The former is the more common mechanism. Circus movement is impulse propagation that traverses a reentrant loop. A circus movement tachycardia is said to have an excitable gap if at some point during the tachycardia cycle, a stimulus can result in premature excitation of the reentrant loop by gaining access to the loop (at the site of the gap). Our understanding of circus movement, and more particularly, the types of paths over which circus movement can occur, is incomplete. Therefore, explanations or descriptions must incorporate simplifying assumptions.[92,93] The first is that the path for the circus movement that underlies reentrant arrhythmias other than fibrillation ordinarily must have adequate central and lateral boundaries to prevent short-circuiting. Second, the length of the path must exceed the wavelength determined by effective refractoriness. Finally, to initiate the circus movement, there must be unidirectional block of the initiating impulse.

These basic requirements can be satisfied in various ways. The central barrier may be anatomical (as in orthodromic reciprocating tachycardia in the Wolff-Parkinson-White syndrome), functional (as in some sustained ventricular tachycardias following myocardial infarction), or combined. Much evidence indicates that many electrophysiological parameters (e.g., conduction) are anisotropic, that is, dependent on direction.[94] Anisotropy is ordinarily determined by fiber orientation such that conduction proceeds most rapidly along the long axis of fibers rather than transversely. Anisotropy may become important in the genesis of some reentrant arrhythmias (Figure 4). The fit between wavelength and path length can be achieved by uniform slowing of conduction along the

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TABLE 4. Continued

Arrhythmia	Mechanisms	Vulnerable parameter	Representative drugs
	Reentry (sodium channel dependent)		
	Long excitable gap		
Atrial flutter type I		Conduction and excitability (depress)	Atrium: sodium channel blocking agents (except lidocaine, mexiletine, tocainide)
Circus movement tachycardia in WPW		Conduction and excitability (depress)	Sodium channel blocking agents (except lidocaine, mexiletine, tocainide)
Sustained monomorphic ventricular tachycardia		Conduction and excitability (depress)	Ventricle: sodium channel blocking agents
	Short excitable gap		
Atrial flutter type II		Refractory period (prolong)	Potassium channel blockers
Atrial fibrillation		Refractory period (prolong)	Potassium channel blockers
Circus movement tachycardia in WPW		Refractory period (prolong)	Amiodarone, sotalol
Polymorphic and sustained monomorphic ventricular tachycardia		Refractory period (prolong)	Quinidine, procainamide, disopyramide
Bundle branch reentry		Refractory period (prolong)	Quinidine, procainamide disopyramide
Ventricular fibrillation		Refractory period (prolong)	Bretylium
	Reentry (calcium channel dependent)		
AV nodal reentrant tachycardia		Conduction and excitability (depress)	Calcium channel blocking agents
Circus movement tachycardia in WPW		Conduction and excitability (depress)	Calcium channel blocking agents
Verapamil-sensitive ventricular tachycardia		Conduction and excitability (depress)	Calcium channel blocking agents

EAD, early afterdepolarization; DAD, delayed afterdepolarization; WPW, Wolff-Parkinson-White syndrome.

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entire path, by local slowing of conduction, or by shortening of the effective refractory period in some or all portions of the reentrant pathway. The slowing of conduction may be a result of primary depression of the excitatory current (I_{Na} or I_{Ca}) or of delineation(s) arising when tissues in the pathway have only incompletely recovered excitability and responsiveness. Slowing might also result from changes in passive properties (membrane resistance or gap junctional resistance) that adversely influence the spread of excitatory current. All these mechanisms might operate in concert in the same or in different parts of the circuit.

Depending on the local speed of propagation of the impulse and the local duration of the effective refractory period, it may be possible to initiate a new impulse in advance of the circulating wavefront. If this is possible, the circuit is said to have an excitable gap.[95,96] If speed of conduction varies as the impulse traverses the circuit, there may be an excitable gap at some sites but not at others. Usually, during the excitable gap there is not full recovery of excitability and thus a prematurely induced impulse will propagate more slowly than the primary circulating impulse.

Reentrant excitation due to circus movement can be terminated in various ways, including premature activation, overdrive pacing (impulses entering the circuit via the excitable gap block both in the antegrade and retrograde direction during the same cycle), and drugs. Most drugs now used are effective because they block conduction by directly reducing

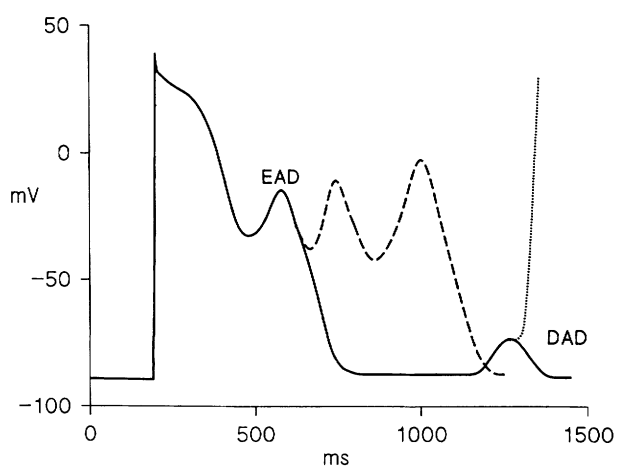

FIGURE 3. *Schematic representation of a transmembrane action potential. Repolarization time course is interrupted by an early afterdepolarization (EAD) and diastole is interrupted by a delayed afterdepolarization (DAD). ---, Repetitive EADS; ···, an action potential upstroke arising from a DAD.*

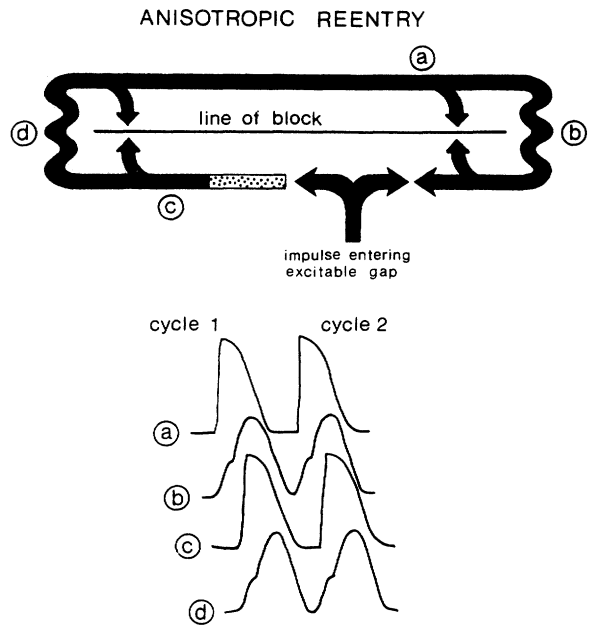

FIGURE 4. *Schematic representation of an anisotropic reentrant circuit. The line of block is parallel to fiber orientation. The part of the circuit that is absolutely refractory is black, the part that is relatively refractory is stippled, and the part that is fully excitable is white. Conduction parallel to the long fiber axis (longitudinal conduction) is fast, and conduction perpendicular to it (transverse conduction) is slow. Only the two longitudinal limbs of the circuit have an excitable gap, as shown by the schematic drawings of the action potentials in both longitudinal limbs (a and c) and at the two pivoting points of transverse conduction (b and d). In b and d, there is no diastolic interval separating repolarization phase and upstroke of the next action potential, whereas this is present in a and c. Therefore, an impulse originating outside the circuit can penetrate the excitable gap only in the longitudinal limbs. It will conduct retrogradely and collide with the oncoming reentrant wavefront. Depending on the state of recovery of the tissue in the antegrade direction, the penetrating impulse may continue in the circuit (resetting or entraining) or block.*

the excitatory current or they delay recovery of responsiveness (prolong the refractory period) (see Figure 5). However, reduction of excitatory current may be a two-edged sword (see Figure 6); in areas with mildly depressed excitability, further impairment of excitability may create unidirectional block and thus facilitate the initiation of reentry. In addition, reduction in conduction velocity in a circuit without block will shorten the wavelength and facilitate reentry. Enhancement of conduction and—under certain circumstances—shortening of refractoriness also may be antiarrhythmic, but these properties do not characterize most currently available drugs.

Fibrillation is characterized by the presence of multiple wavefronts of excitation. These multiple wavefronts engage either partially or absolutely refractory tissue, and the changing course of the wavefronts is dictated by the available corridors of responsive tissue. Persistence of fibrillation depends on the presence of a critical number of simultaneous wavefronts.[97] Prolongation of the effective refractory period is a beneficial countermeasure (other than electrical countershock) because it will reduce the number of simultaneously present wavefronts (see Figure 5).

The suppression of reentry generally is accomplished by one of the many agents that predictably and consistently alter conduction and/or refractoriness, the two vulnerable parameters. Recently, the role of intercellular connections (gap junctions) contributing to the slowing and/or block of conduction in reentrant circuits has been emphasized. A relative sparsity of intercellular connections promotes conduction slowing and/or block in some experimental models of reentry.[98] This factor has not been incorporated explicitly in the classification because no practical therapeutic intervention has been identified; however, a category for agents that influence gap junctions could be added later.

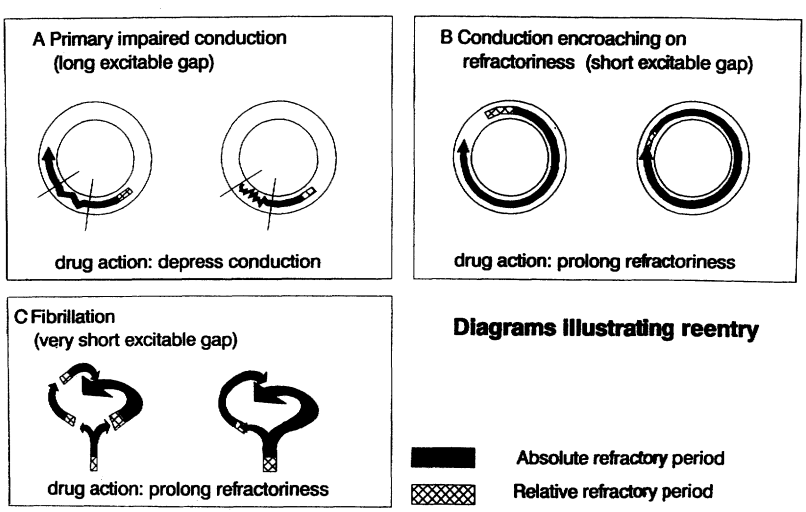

FIGURE 5. *Schematic representation of reentry and the ways to terminate reentry. In* panel A, *there are impaired conduction and excitability in a segment of the reentrant circuit (delineated by the two lines). Further depression of conduction and excitability will result in conduction block in that segment. As a precondition in* panel B, *conduction during the reentrant tachycardia encroaches on the relative refractory period. Prolongation of refractoriness will cause block of the reentrant wavefront in its own refractory tail (or the impulse may merely slow down). In* panel C, *fibrillation is maintained by the presence of many independent wavefronts. Prolongation of the wavelength of refractoriness reduces the number of wavefronts in a given chamber below a critical number; block and collision terminate the arrhythmia.*

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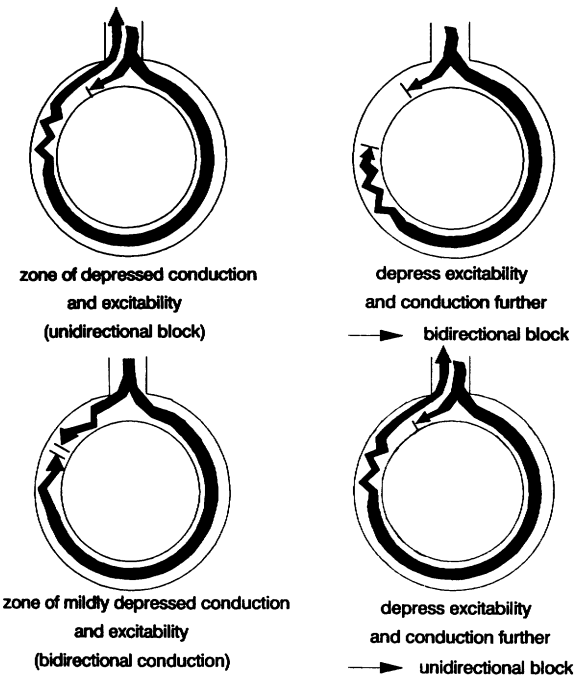

FIGURE 6. *Diagram illustrating how depression of excitability and conduction may either prevent or promote the initiation of reentry. In the* upper left panel, *excitability and conduction in a segment are depressed so that unidirectional block sets the stage for induction of reentry by a premature impulse entering the circuit. In the* upper right panel, *excitability and conduction are further impaired, creating a zone of bidirectional block so that reentry can no longer be initiated. In the* lower left panel, *the segment is only mildly depressed. Bidirectional conduction is responsible for collision of wavefronts (causing bidirectional block). Further depression creates the setting for unidirectional block* (lower right panel).

Other mechanisms. We have included these mechanisms for the sake of completeness but will not consider them extensively in terms of vulnerable parameters and drug actions.

REFLECTION. In a nonbranching bundle, an impulse returning over the same bundle may result from reentry based on longitudinal dissociation within the bundle or from reflection.[99] Reflection may be caused by electrotonic transmission across an inexcitable segment in a linear bundle. The delay in impulse transmission, if long enough, allows fibers proximal to the inexcitable segment to recover their excitability and be available for excitation by current flowing retrogradely across the inexcitable zone. Reflection has been identified in isolated cardiac tissues studied using interventions such as the sucrose gap. It is uncertain whether it occurs in the intact heart.

PARASYSTOLE. Parasystole is caused by a mechanism for abnormal impulse initiation, usually thought to be automatic, whose expression is determined by the presence and extent of entrance and exit block.[100] For example, an automatic focus in a strand of Purkinje fibers may be surrounded by a small rim of inexcitable fibers that are only capable of transmitting electrotonic currents. Normal sinus impulses are not able to directly excite the focus (the focus is "protected") but can produce subthreshold depolarizations that, depending on their timing with respect to the intrinsic cycle of the automatic focus, delay or accelerate automatic firing. Automatic impulses may excite the tissue proximal to the depressed segment and be a cause for extrasystoles.[100] Whereas parasystole is generally thought to be benign, it could conceivably provide a trigger for sustained reentrant rhythms.

Heart Rate Dependency

Heart rate is a critical determinant of the electrophysiological behavior of normal and abnormal cardiac tissues and their response to drugs. Interventions that can be antiarrhythmic at one heart rate may be ineffective or even provoke arrhythmias at a different rate.

Whether a premature beat is effective as a trigger for a reentrant arrhythmia may depend on both underlying heart rate and the degree of prematurity. It has been suggested that whether parasystolic impulses become manifest depends on the relation of underlying heart rate and the intrinsic rate of the ectopic focus. Electrotonic transmission and reflection are critically dependent on heart rate; drugs that improve transmission across an inexcitable gap may shift the reflection zone to higher rates and prevent reflection at slower rates. On the other hand, drugs that impair transmission across an inexcitable gap abolish reflected extrasystoles at fast heart or stimulation rates and promote them at slow rates.[101,102]

The combined effects of sodium channel blocking agents and heart rate may explain why in the setting of experimental acute ischemia, lidocaine has been reported both to be antifibrillatory[103] and to increase the incidence of ventricular fibrillation.[104] In zones of mildly depressed conduction and excitability, sodium channel blockers may at rapid rates create zones of unidirectional block and thus promote the initiation of reentrant rhythms. In areas of severely depressed excitability and conduction, such a combination may create zones of complete inexcitability that may prevent reentry or facilitate circus movement by providing an inexcitable central barrier (see Figure 6). Since binding of some drugs to and dissociation from their targeted ion channels are well recognized to be rate- (and voltage-) dependent, the effects of sodium channel blockers can be expected to be more pronounced at fast rates, especially in partially depolarized fibers such as those present in acute ischemia. An exception is open-channel binding, which decreases with increasing inactivation. Drugs that rapidly increase their binding to (and block of) sodium channels with an increase in rate ("fast on") may in theory be more effective in preventing tachycardia onset, while "slow on" drugs may terminate tachycardias more effectively, after many beats.

Drugs that prolong action potential duration usually have their greatest effects at slow rates[56] (where they also may be toxic, by generating triggered activ-

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ity from early afterdepolarizations). In theory, such drugs may become less effective in preventing or terminating reentrant rhythms as the rates of the tachycardias increase; however, experimental data suggest a prominent antifibrillatory role for drugs that prolong the action potential.

Arrhythmias and Antiarrhythmic Drugs in the Clinical Setting

Arrhythmias in the Human Heart: Relation to Basic Experimental Information

For many common clinical arrhythmias (e.g., atrial fibrillation and flutter, AV nodal reentry and circus movement tachycardia in the Wolff-Parkinson-White syndrome, many ventricular tachycardias and ventricular fibrillation) the mechanisms have been generally well characterized[95,96,105] or are sufficiently supported by data to justify selection of a therapeutic drug regimen. However, in individual cases, especially the majority of ventricular tachycardias, it is rarely if ever possible to be able to define the anatomic and functional properties of a reentrant circuit sufficiently to permit specific drug selection. Moreover, interpatient variability of drug effects, the effects of metabolites, and the effects of disease on drug distribution all can modify drug action. The result is that the best that can be expected of a classification is that it provide a relatively small set of reasonable options for therapy rather than a single optimal choice and bring order and logic to therapy.

Certain clinical arrhythmias may result from more than one mechanism because different mechanisms may operate at onset and during maintenance (e.g., EAD triggering nonsustained ventricular tachycardia or inducing reentrant ventricular tachycardia or fibrillation) or because different variants of a mechanism may operate in the same arrhythmia (e.g., reentry with sodium-dependent conduction in one part of the circuit and calcium-dependent conduction in another part, as seen in circus movement tachycardia in the Wolff-Parkinson-White syndrome). For any given ventricular tachycardia it may not be clear whether conduction is primarily impaired in different parts of the circuit, with a long excitable gap, or impaired because of encroachment on refractoriness, or both. There is evidence that some ventricular tachycardias depend on calcium current for reentrant excitation, others on EAD or DAD. Thus, in Table 4 ventricular tachycardia appears in various categories.

We recognize that the information contained in Table 4 is complex and not readily memorized. However, the purpose of our deliberations was not to provide an overly simplified system for the classification of drug actions, but rather to provide a system that permits rational understanding to promote research and systematic analyses. Nonetheless, the actual mechanisms whereby drugs may act—in light of a vulnerable parameter—can be considered in simpler fashion than that which is demonstrated in Tables 3 and 4, because the mechanisms for arrhythmias are rather few. Hence, the classification of drug actions in Tables 3 and 4 can be considered in light of the mechanisms as they are summarized in Table 5. In considering Table 5, it must be understood that the use of a term in relation to an antiarrhythmic action would imply an action countering the mechanism, not an action promoting it. For convenient use, each drug action could be described by a short term or expression, for example, drugs countering "automaticity," "triggering," "Na^+ reentry," and "Ca^{2+} reentry." The separation of the sodium-dependent reentry class into subdivisions, depending on whether excitatory current or refractoriness is the critical (and vulnerable) parameter, is based on the long-appreciated critical roles of conduction and refractoriness in the mechanism of reentry, the ready availability of agents that affect predominantly each of these properties by fundamental actions on sodium or potassium channels, and the separation of these classes of agents in the Vaughan Williams classification. It is recognized that often both conduction and refractoriness may be "critical" in the same circuit; often it is not possible to determine the critical parameter in an individual case, especially in ventricular tachycardia; and even when encroachment on refractoriness is critical, agents depressing excitatory currents may be effective. Thus, selection for the group "sodium-reentry-long gap" (sodium channel blockers) versus "sodium-reentry-short gap" (potassium channel blockers) will often be arbitrary. However, these categories, so designated, may encourage clinical investigations of the responses of the circuit to determine the critical parameter, for example, by analyzing the responses of appropriate sites to programmed stimulation.

TABLE 5. Classification of Arrhythmogenic Mechanisms

Automaticity
Enhanced normal
Abnormal
Triggering
EAD
DAD
Na^+-Dependent reentry
Primary impaired conduction (long excitable gap)
Conduction impaired by refractoriness (short excitable gap)
Ca^{2+}-Dependent reentry
Reflection
Parasystole

EAD, early afterdepolarization; DAD, delayed afterdepolarization.

Clinical Approach to the Use of Antiarrhythmic Drugs

To a large extent, the management of clinical cardiac arrhythmias requires the use of antiarrhythmic drugs. Nonetheless, concerns about the long-term efficacy, safety, and cost-effectiveness of pharmacological therapy[106–108] have resulted in a movement toward the use of nonpharmacological methods of treat-

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ment,[109,110] such as those based on devices or ablation management strategies for selected arrhythmias. However, drugs are likely to remain in a mainstay of therapy for the majority of patients with cardiac arrhythmias.

Today the physician may choose from among 30 to 80 agents being tested or marketed for the control of cardiac arrhythmias, and in the near future many new drugs will become available. Each of these drugs has a unique profile of action, and none is uniformly effective and free of adverse effects. In clinical practice, drugs are chosen in order to achieve efficacy without encountering unacceptable side effects. The basis for this choice may be past experience, fashion, protocol, or antiarrhythmic drug classification.[111,112]

At times the physician may know the mechanism of the tachycardia and can design specific therapy. For example, the regular, narrow QRS complex tachycardia usually seen in association with the Wolff-Parkinson-White syndrome is due to reentry over a large circuit with two potentially vulnerable segments (AV node and accessory atrioventricular connection), which may be assessed by clinical electrophysiological techniques. The mechanism that triggers initiation of the tachycardia (atrial or ventricular ectopic activity, etc.) can sometimes be assessed by long-term ECG monitoring. Armed with this information, the clinician can prescribe therapy specifically to abolish the trigger mechanism or, preferably, adjust the substrate to prevent initiation or continuation of reentry. The latter may be achieved by choosing drugs that impair slow AV nodal conduction (calcium channel dependent), such as digitalis glycosides, β-adrenergic blockers or calcium channel blockers, or drugs that retard fast conduction through the accessory atrioventricular connection (sodium channel dependent) such as flecainide or procainamide.

The mechanisms of many other arrhythmias are less clear.[112] For example, atrial tachycardia may be caused by reentry, abnormal automaticity, or triggered activity. Clinical clues may suggest a specific mechanism toward which therapy may be targeted, but if the mechanism remains in doubt, the physician may opt to offer treatment speculatively, on the basis of the relative likelihood of the operation of a particular mechanism.

To choose a particular drug or drug combination to treat specific arrhythmias, the physicians must not only understand the putative mechanism of the arrhythmia (see for example Table 3) but must also appreciate the wide range of antiarrhythmic drug actions that are available as shown in Table 4. The tabulated presentation of the drug actions in Table 4 has been enlarged on in Figure 7. This listing incorporates several important principles:

1) The listing is flexible—no numbers or letters are used as shorthand descriptors of drug actions.

2) The drugs are not placed within one or more cells of a catalogue. Rather, they are listed in the first column of a row and their important actions are indicated in the other cells in that row.

3) The vertical order of the antiarrhythmic drugs may be changed to emphasize different drug clusters. For example, drugs that act at the β-receptor could be placed together, and the different actions of these drugs on other receptors, channels, and pumps would then become more readily apparent. Hence, one can collate specific major drug actions in light of a particular vulnerable parameter and then consider the associated actions of the various drugs and the risks or benefits these may entail.

Concluding Remarks

In summary, the collation of clinical and electrocardiographic information allows the physician to reach a descriptive diagnosis of a cardiac arrhythmia. This diagnosis may imply, with variable certainty, an arrhythmia mechanism that suggests a particular treatment. Effective pharmacological therapy requires that the physician attempt to identify a drug with the most appropriate profile to attack the most vulnerable parameter of the mechanisms of the cardiac arrhythmia. As information about the mechanisms of clinical cardiac arrhythmias becomes more complete, the actions of antiarrhythmic drugs are more fully understood, and the number and variety of antiarrhythmic drugs increases, specific pharmacological management of cardiac arrhythmias will progressively improve. In the meantime, the series of tables and figures provided here, incorporating the beginnings of a classification based on arrhythmogenic mechanism and the identification of vulnerable parameters, provides a basis not only for rational consideration of arrhythmias and their therapy, but for communication among basic and clinical investigators and practicing physicians. Hence, a groundwork for continued growth and incorporation of knowledge is provided.

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Appendix

This paper summarizes the outcome of a workshop held in Taormina, Sicily, December 1–4, 1990. The need for the workshop was proposed by Peter J. Schwartz and Michiel J. Janse. It was organized by the Working Group on Arrhythmias of the European Society of Cardiology, with joint sponsorship by the Basic Science Council of the American Heart Association and the American College of Cardiology. Its funding was administered by the European Society of Cardiology. The workshop was chaired by Michael R. Rosen. Participating in the workshop and coauthoring the paper were J. Thomas Bigger Jr., Günter Breithardt, Arthur M. Brown, A. John Camm, Edward Carmeliet, Harry A. Fozzard, Brian F. Hoffman, Michiel J. Janse, Ralph Lazzara, Alessandro Mugelli, Robert J. Myerburg, Dan M. Roden, Michael R. Rosen, Peter J. Schwartz, Harold C.

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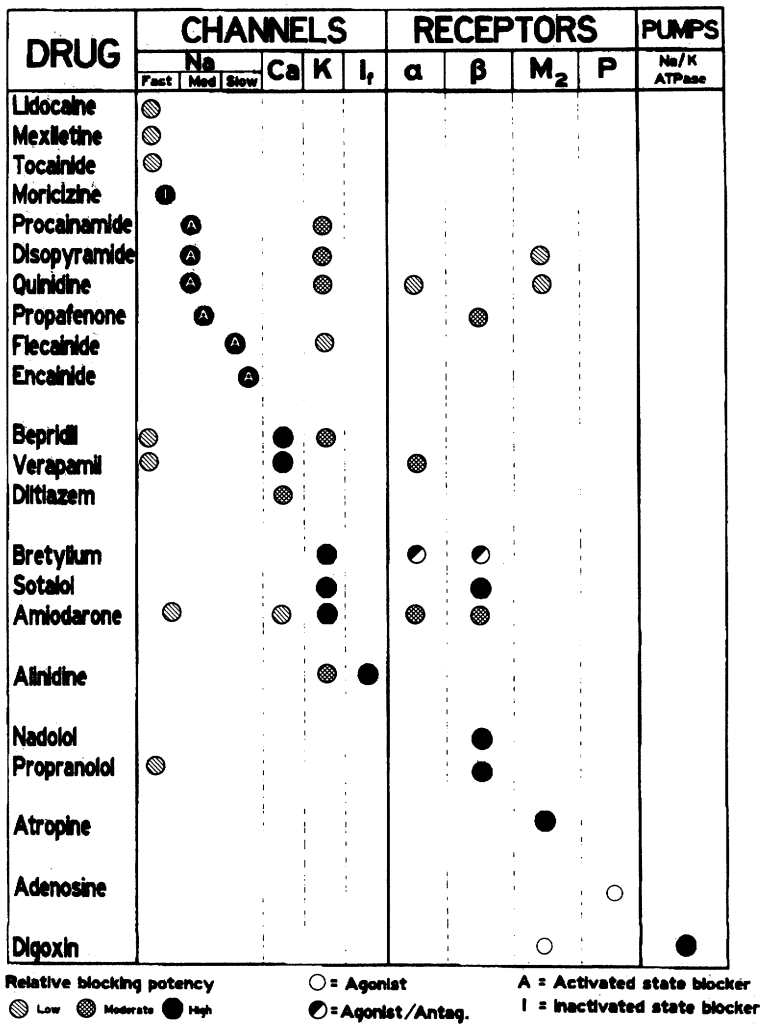

FIGURE 7. *Summary of the potentially most important actions of drugs on membrane channels, receptors, and ionic pumps in the heart. Included are examples of drugs used to modify cardiac rhythm. Most are already marketed as antiarrhythmic agents, but some are not yet approved for this purpose. The drugs (rows) are ordered in a fashion similar to the columns so that generally the entries for their predominant action(s) form a diagonal. Drugs with multiple actions (e.g., amiodarone) depart strikingly from the diagonal trend. The actions of drugs on the sodium, calcium, potassium (I_K), and I_f channels are indicated. Sodium channel blockade is subdivided into three groups of actions characterized by fast (<300 msec), medium (Med) (200–1,500 msec) and slow (>1,500 msec) time constants for recovery from block. This parameter is a measure of use dependence and predicts the likelihood that a drug will decrease conduction velocity of normal sodium-dependent tissues in the heart and perhaps the propensity of a drug for causing bundle-branch block or proarrhythmia. The rate constant for onset of block might be even more clinically relevant. Blockade in the inactivated (I) or activated (A) state is indicated. Information on the state dependency of the block caused by moricizine, propefenone, encainide, and flecainide is especially limited and may be altered with additional research. Drug interaction with receptors (α, β, muscarinic subtype 2 [M_2], and A_1 purinergic [P]) and drug effects on the sodium/potassium pump (Na/K, ATPase) are indicated. Filled circles indicate antagonist or inhibitory actions; unfilled circles indicate direct or indirect acting agonists or stimulators. The darkness of the symbol increases with the intensity of the action. Half-filled circles for bretylium indicate its biphasic action to initially stimulate α- and β-receptors by release of norepinephrine followed by subsequent block of norepinephrine release and indirect antagonism of these receptors.*

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KEY WORDS • Point of View • antiarrhythmic drug classification • vulnerable parameter

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